FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE' ENTERED AT 11:04:55 ON 01 AUG 2002

L1 476734 INTERLEUKIN
L2 18869 INTERLEUKIN (W) 5
L3 18398 IL (W) 5
L4 73256 ANTISENSE
L5 14496 RIBOZYME
L6 97 L1 AND L2 AND L3 AND L4

=> dup rem
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L7 40 DUP REM L6 (57 DUPLICATES REMOVED)
ANSWERS '1-19' FROM FILE BIOSIS
ANSWERS '20-31' FROM FILE MEDLINE
ANSWERS '32-38' FROM FILE CAPLUS
ANSWERS '39-40' FROM FILE EMBASE

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L7 ANSWER 1 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:269657 BIOSIS
DOCUMENT NUMBER: PREV200200269657
TITLE: Inhibition of antigen-induced eosinophilia and airway hyperresponsiveness by **antisense** oligonucleotides directed against the common beta chain of IL-3, **IL-5**, GM-CSF receptors in a rat model of allergic asthma.
AUTHOR(S): Allakhverdi, Zoulfia; Allam, Mustapha; Renzi, Paolo M. (1)
CORPORATE SOURCE: (1) CHUM Research Center, 2065 Alexandre de Seve, 8th floor, Montreal, Quebec, H2L 2W5: renzip@earthlink.net Canada
SOURCE: American Journal of Respiratory and Critical Care Medicine, (April 1, 2002) Vol. 165, No. 7, pp. 1015-1021. print. ISSN: 1073-449X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Airway obstruction, hyperresponsiveness, and the accumulation and persistence within the airways of inflammatory cells characterize asthma. **Interleukin** (IL)-3, granulocyte macrophage colony-stimulating factor (GM-CSF), and **IL-5** are among several cytokines that have been shown to be increased in asthma and to contribute to atopic inflammation. They mediate their effect via receptors that have a common beta subunit (betac). We hypothesized that blocking of this common betac would impair the airway response to antigen. We report that an **antisense** (AS) phosphorothioate oligodeoxynucleotide (ODN) found to specifically inhibit transcription of the betac in rat bone marrow cells also caused inhibition of betac mRNA expression and of immunoreactive cells within the lungs of Brown Norway (BN) rats when injected intratracheally ($p < 0.01$). Inhibition of betac significantly reduced ($p < 0.01$) experimentally induced eosinophilia in vivo in ovalbumin (OVA)-sensitized BN rats after antigen challenge. Furthermore, when compared with mismatch-treated rats, betac AS-ODN caused inhibition of antigen-induced airway hyperresponsiveness to leukotrine D4. Taken together, our findings demonstrate that the common betac of IL-3, **IL-5**, and GM-CSF receptors is involved in the eosinophil influx and airway hyperresponsiveness that follow OVA challenge and underscore the potential utility of a topical **antisense** approach targeting betac for the treatment of asthma.

L7 ANSWER 2 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2002:406489 BIOSIS
DOCUMENT NUMBER: PREV200200406489

TITLE: Asthma therapy in the new millennium.
AUTHOR(S): Pahl, A. (1); Szelenyi, I.
CORPORATE SOURCE: (1) Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-University of Erlangen, Fahrstr. 17, DE-91054, Erlangen: pahl@pharmakologie.uni-erlangen.de Germany
SOURCE: Inflammation Research, (June, 2002) Vol. 51, No. 6, pp. 273-282. http://www.birkhauser.ch/journals/1100/1100_tit.htm. print.
ISSN: 1023-3830.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB Bronchial asthma is one of the most common chronic diseases in modern society and yet, despite the availability of highly effective drugs, there is increasing evidence to suggest that its incidence is increasing. It is a general health problem in several industrialised countries and will remain one for the next decades. With regard to asthma pathogenesis, our understanding has increased tremendously over the last two decades. Therefore, the potential for specific targeted and constructed therapies has become evident. Monoclonal antibodies to IgE, soluble receptors or antibodies to certain cytokines such as IL-4 and **IL-5** are being investigated as possible treatments for asthma. Besides the already known receptor antagonists, new compounds directed to novel receptor types (e.g. cytokine, adenosine, adhesion molecules, etc.) are now under development. New targets in the cytosol will come into focus. Preliminary studies of selective phosphodiesterase (PDE) inhibitors in asthmatic patients have been encouraging. It is also very likely that the use of glucocorticoids cannot be excluded from therapy. However, we should generate new glucocorticoids with less side-effects, probably by using the so-called retrometabolic drug design. The first representative of this new steroid class, loteprednol is already approved for the therapy of certain allergic disorders. Because asthma is a disease of many different gene polymorphisms, gene therapy seems to be of low success at present. Alternatively, **antisense** oligonucleotides could be used. Future developments may also include strategies targeting the remodeling of structural elements of the airways. Today's intensive search for new treatments should ensure a greater diversity of therapeutic possibilities for the management of asthma in the next millennium.

L7 ANSWER 3 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 2001:327469 BIOSIS
DOCUMENT NUMBER: PREV200100327469
TITLE: Grass pollen immunotherapy: Symptomatic improvement correlates with reductions in eosinophils and **IL-5** mRNA expression in the nasal mucosa during the pollen season.
AUTHOR(S): Wilson, Duncan R.; Nouri-Aria, Kayhan T.; Walker, Samantha M.; Pajno, Giovanni B.; O'Brien, Fiona; Jacobson, Mikila R.; Mackay, Ian S.; Durham, Stephen R. (1)
CORPORATE SOURCE: (1) Upper Respiratory Medicine, Imperial College School of Medicine at The National Heart and Lung Institute, Dovehouse St, London, SW3 6LY UK
SOURCE: Journal of Allergy and Clinical Immunology, (June, 2001) Vol. 107, No. 6, pp. 971-976. print.
ISSN: 0091-6749.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: Tissue eosinophilia and infiltration by TH2-type T cells are characteristic features of allergic rhinitis both after allergen challenge and during natural allergen exposure. Specific immunotherapy inhibits allergen-induced nasal eosinophilia. Objectives: We sought to assess, in the context of a randomized trial, the relationships between symptomatic

improvement after immunotherapy and eosinophil numbers and **IL-5** expression in the nasal mucosa during the pollen season. Methods: Nasal biopsy specimens were taken from 37 adults with severe summer hay fever at baseline (out of season) and at peak season after 2 years of treatment with a depot grass pollen extract or placebo. Biopsy specimens were processed for immunohistochemistry by using mAbs against eosinophils (EG2), T cells (CD3), and IL-2 receptor-positive cells (CD25), as well as for in situ hybridization by using a sulfur 35-labeled **antisense** riboprobe directed against **IL-5**. Results: Immunotherapy significantly reduced symptoms (49%, P=.01) and medication requirements (80%, P=.007) compared with placebo. There was a 400% increase (P=.004) in eosinophils during the pollen season in placebo-treated patients, which was inhibited in the immunotherapy group (20% increase, P=.04 between groups). Seasonal increases were also observed for CD25+ cells (P=.002), CD3+ cells (P=.02), and **IL-5** mRNA-expressing cells (P=.03) in the placebo group but not in the immunotherapy group. A significant correlation was observed between eosinophils and **IL-5** expression (r=0.5, P<.05). Both eosinophils (r=0.6, P<.02) and **IL-5** (r=0.6, P<.02) correlated with symptoms after immunotherapy. Conclusion: Improvement in symptoms after grass pollen immunotherapy may result, at least in part, from inhibition of **IL-5**-dependent tissue eosinophilia during the pollen season.

L7 ANSWER 4 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

ACCESSION NUMBER: 2001:567875 BIOSIS
DOCUMENT NUMBER: PREV200100567875
TITLE: Inhibition of GM-CSF/IL-3/**IL-5** signaling by **antisense** oligodeoxynucleotides targeting the common beta chain of their receptors.
AUTHOR(S): Allam, Mustapha; Renzi, Paolo M. (1)
CORPORATE SOURCE: (1) CHUM, Research Center, Notre-Dame Hospital, 2065 Alexandre de Seve, Room Z-8905, Montreal, PQ, H2L-2W5: renzip@earthlink.net Canada
SOURCE: Antisense & Nucleic Acid Drug Development, (October, 2001) Vol. 11, No. 5, pp. 289-300. print. ISSN: 1087-2906.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Granulocyte-macrophage colony-stimulating factor (GM-CSF), **interleukin**-3 (IL-3), and **IL-5** play a key role in allergic inflammation. They mediate their effect via receptors that consist of two distinct subunits, a cytokine-specific alpha subunit and a common beta subunit (betac) that transduces cell signaling. We sought to downregulate the biologic activities of GM-CSF, IL-3, and **IL-5** simultaneously by inhibiting betac mRNA expression with **antisense** technology. Experiments were performed with TF-1 cells (a human erythroleukemia cell line expressing GM-CSF, IL-3, and **IL-5** receptors, which proliferates in response to these cytokines), monocytic U937 cells, which require these cytokines for differentiation, and purified human eosinophils. Cells were treated with **antisense** phosphorothioate oligodeoxynucleotides (ODN) targeting betac mRNA. In contrast to non-treated cells and cells treated by sense or mismatched ODN, **antisense** ODN inhibited betac mRNA expression and significantly decreased the level of cell surface betac protein expression on TF-1 and U937 cells. Receptor function was also affected. **Antisense** ODN were able to inhibit TF-1 cell proliferation in vitro in the presence of GM-CSF, IL-3, or **IL-5** in the culture medium and eosinophil survival. We suggest that **antisense** ODN against betac may provide a new therapeutic alternative for the treatment of neoplastic or allergic diseases associated with eosinophilic inflammation.

L7 ANSWER 5 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8

ACCESSION NUMBER: 2001:233510 BIOSIS
DOCUMENT NUMBER: PREV200100233510
TITLE: The role of STAT1 in activation of IL-3- and **IL-5**-induced eosinophils by interferon gamma.
AUTHOR(S): Ochiai, K. (1); Otaka, K.; Ito, M.; Tomioka, H.
CORPORATE SOURCE: (1) Department of Internal Medicine, Toho University School of Medicine, Sakura Hospital, 564-1 Shimoshizu, Sakura City, 285-8741: kochiai-kkr@umin.ac.jp Japan
SOURCE: International Archives of Allergy and Immunology, (January March, 2001) Vol. 124, No. 1-3, pp. 237-241. print. ISSN: 1018-2438.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Tyrosine phosphorylation of STAT1alpha in eosinophils after IFN-gamma stimulation has been shown, but the biological significance of eosinophil STAT1alpha activation in transmitting the signals through the IFN-gamma receptor remains unknown. The purpose of this study is to determine whether STAT1 is involved in the regulation of eosinophils by IFN-gamma-IFN-gamma receptor interaction. rhIL-3- and rhIL-5-induced eosinophils from CD34+ cells of cord blood on day 28 of culture were used. The cells were washed and further incubated in IL-3- and **IL-5**-free medium for 48 h. The induced eosinophils constitutively expressed CD69 and lost this expression after a further 48-hour incubation without the cytokines. IFN-gamma significantly upregulated CD69 expression on the 48-hour incubated cells. In inhibitory experiments on STAT1, a phosphorothioate oligo **antisense** DNA against STAT1alpha was added to IL-3- and **IL-5**-containing medium from day 15 to day 28 of culture. The oligo DNAs altered neither the expressions of myeloid cell marker CD9 and 13 nor the expression of IFN-gamma receptor on the cells. The added STAT1alpha **antisense**, but not sense, DNA significantly reduced STAT1alpha mRNA expression in the cells. The STAT1 **antisense** also significantly inhibited IFN-gamma-induced CD69 expression on the 48-hour incubated eosinophils. In conclusion, these results indicate that IFN-gamma induces CD69 expression in the induced eosinophils through STAT1alpha, suggesting that STAT1alpha may play a significant role in eosinophil regulation by IFN-gamma.

L7 ANSWER 6 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9

ACCESSION NUMBER: 2001:152779 BIOSIS
DOCUMENT NUMBER: PREV200100152779
TITLE: In vitro and in vivo inhibition of **interleukin** (**IL**)-**5**-mediated eosinopoiesis by murine IL-5Ralpha **antisense** oligonucleotide.
AUTHOR(S): Lach-Trifilieff, Estelle; McKay, Robert A.; Monia, Brett P.; Karras, James G.; Walker, Christoph (1)
CORPORATE SOURCE: (1) Novartis Horsham Research Centre, Wimblehurst Road, Horsham, RH12 5AB: christoph.walker@pharma.novartis.com UK
SOURCE: American Journal of Respiratory Cell and Molecular Biology, (February, 2001) Vol. 24, No. 2, pp. 116-122. print. ISSN: 1044-1549.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The unique role of **interleukin** (**IL**)-**5** in eosinophil production, activation, and localization makes this cytokine a prime target for therapeutic intervention in diseases characterized by a selective blood and tissue eosinophilia. In an attempt to block the effects of **IL-5** on eosinophils, a strategy was developed to suppress the expression of the **IL-5**

receptor alpha chain (IL-5Ralpha) by **antisense** oligonucleotides (ASOs). IL-5Ralpha ASOs were identified which selectively and specifically suppress the expression of messenger RNA and proteins of both the membrane and the soluble form of the receptor in constitutively IL-5R-expressing murine BCL-1 cells in vitro. Moreover, these IL-5Ralpha-specific ASOs were able to selectively inhibit the **IL-5**-induced eosinopoesis from murine fetal liver and bone marrow cells in vitro, suggesting that these molecules may affect the development of **IL-5**-mediated eosinophilia in vivo. Indeed, intravenous administration of IL-5Ralpha-specific ASOs not only suppressed the bone-marrow and blood eosinophilia in mice after short-term treatment with recombinant murine **IL-5** but also inhibited the development of blood and tissue eosinophilia in a ragweed-induced allergic peritonitis model. Thus, blocking the expression of IL-5Ralpha on eosinophil using ASOs may have therapeutic benefits in eosinophilic diseases such as asthma.

L7 ANSWER 7 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 12

ACCESSION NUMBER: 2001:122585 BIOSIS
DOCUMENT NUMBER: PREV200100122585
TITLE: Experimental study on treatment of bronchial asthma with **antisense** oligonucleotid.
AUTHOR(S): Wang Mei-qin (1); Bai Chun-xue (1); Niu Shan-fu (1); Fang Xiao-hui (1); Chen Chang-qing; Chen Bo
CORPORATE SOURCE: (1) Institute of Respiratory Disease, Zhongshan Hospital, Shanghai Medical University, Shanghai, 200032 China
SOURCE: Journal of Shanghai Medical University, (Nov., 2000) Vol. 27, No. 6, pp. 464-467, 470. print.
ISSN: 0257-8131.
DOCUMENT TYPE: Article
LANGUAGE: Chinese
SUMMARY LANGUAGE: Chinese; English

AB Purpose To explore the possibility and the effect of therapeutic bronchial asthma by **antisense** oligonucleotid. Methods Based on the **IL-5** cDNA sequence of mouse, a segment of **antisense** oligonucleotid was designed and synthetized. 5'-labeling of **antisense** oligonucleotid was signed by T4 PNK in order that the efficiency of stearylamine liposome in transfe-ting **antisense** oligonucleotid can be evaluated. Astham model was duplicated with ovalbumin (OVA) absorbed to aluminum hydroxide. T lymphocytes of mice were separated by nylon fiber method, then T lymphocytes transfected a different content of **antisense** oligonucleotid with stearylamine phys. positive liposome were cultured respectively in order to observe the effect of **antisense** oligonucleotid on **IL-5** produced by T lymphocytes. **IL-5** levels in the supernatants of T lymphocytes culture were determined by ELISA. Results Stearylamine liposome could markedly increase the efficiency of **antisense** oligonucleotid transfection. The efficiency of **antisense** oligonucleotid transfection was the best at 1:15 m/m (**antisense** oligonucleotid and SA liposome) and it was increased approximately 12 times. In healthy and asthma Balb/c mice, **IL-5** was not detected in the supernatants of T lymphocytes culture without challenge with OVA. However, **IL-5** was increased markedly in the supernatants of T lymphocytes culture challenged with OVA. After transfecting a different concentration **antisense** oligonucleotid, **IL-5** levels in the supernatants of T lymphocytes culture were significantly lower than those in control cells without **antisense** oligonucleotide transfection. **IL-5** levels decreased from (44.60 +- 6.23) to (30.70 +- 7.362), (17.20 +- 6.181) and (8.16 +- 2.34) pg/ml respectively. And **IL-5** synthesis was inhibited by 31.17%, 61.43% and 81.7% respectively. Conclusions **IL-5** synthesis could be obviously inhibited by **antisense** oligonucleotid and showed a

markedly relation between quantitative and effect. It is supported that the production of **IL-5** be inhibited through preventing the transcription of **IL-5** from T lymphocytes. The study provides foundation for **antisense** gene therapeutic asthma.

L7 ANSWER 8 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 13

ACCESSION NUMBER: 2000:398525 BIOSIS
DOCUMENT NUMBER: PREV200000398525
TITLE: Deletion of individual exons and induction of soluble murine **interleukin-5** receptor-alpha chain expression through **antisense** oligonucleotide-mediated redirection of pre-mRNA splicing.
AUTHOR(S): Karras, James G. (1); McKay, Robert A.; Dean, Nicholas M.; Monia, Brett P.
CORPORATE SOURCE: (1) Department of Molecular and Cellular Pharmacology, Isis Pharmaceuticals, 2292 Faraday Ave., Carlsbad, CA, 92008 USA
SOURCE: Molecular Pharmacology, (August, 2000) Vol. 58, No. 2, pp. 380-387. print.
ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Expression of the **interleukin-5** receptor-alpha (IL-5Ralpha) chain is thought to play an important role in the pathogenesis of asthma and other eosinophilic diseases. With **antisense** oligonucleotides (ASOs) chemically modified to provide increased hybridization affinity for RNA but that do not support RNase H-mediated cleavage (2'-O-methoxyethyl-modified ASOs), we show that constitutive splicing of murine IL-5Ralpha mRNA can be modulated in cells such that individual exons may be selectively deleted from mature transcripts. Specific deletion of individual exons and redirection of alternative splicing of the IL-5Ralpha mRNA have been achieved with this approach, by targeting 3'-splice sites or exon sequences immediately downstream of an alternative splice site. ASO targeting with these strategies resulted in inhibition of mRNA and protein levels of the membrane IL-5Ralpha isoform capable of signaling **IL-5** -mediated growth and antiapoptotic signals to eosinophils. Membrane isoform IL-5Ralpha inhibition was coupled with an increase in expression of mRNA for the alternatively spliced soluble isoform, which binds **IL-5** extracellularly and may block its function. These observations suggest the potential general therapeutic use of an **antisense** approach to increase expression of variant RNA transcripts and to thereby produce proteins devoid of specific functional domains that may impact disease processes, as well as its specific utility for modulating expression of a key cytokine receptor implicated in allergic inflammation.

L7 ANSWER 9 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 14

ACCESSION NUMBER: 2001:812 BIOSIS
DOCUMENT NUMBER: PREV200100000812
TITLE: **Antisense** inhibition of membrane-bound human **interleukin-5** receptor-alpha chain does not affect soluble receptor expression and induces apoptosis in TF-1 cells.
AUTHOR(S): Karras, James G. (1); McKay, Robert A.; Lu, Tao; Dean, Nicholas M.; Monia, Brett P.
CORPORATE SOURCE: (1) Department of Molecular and Cellular Pharmacology, ISIS Pharmaceuticals, 2292 Faraday Avenue, Carlsbad, CA, 92008 USA
SOURCE: Antisense & Nucleic Acid Drug Development, (October, 2000) Vol. 10, No. 5, pp. 347-357. print.
ISSN: 1087-2906.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Binding of human **interleukin-5** (HuIL-5) to its membrane-anchored receptor (IL-5R) triggers multiple signaling pathways, cellular proliferation, and maturational responses, as well as protection from apoptosis. In contrast, soluble forms of the HuIL-5R have been shown to inhibit **IL-5** signaling and, therefore, may represent naturally occurring negative regulators of **IL-5** function. Because of the central role of **IL-5** in promoting eosinophilia and airway hyperresponsiveness in animal models of asthma, **antisense** oligonucleotides specific either for the membrane form alone or for sequences shared between both the membrane and soluble forms of the HuIL-5Ralpha ligand binding chain were designed. The activities of these oligonucleotides were characterized in IL-5R-expressing erythroleukemic TF-1 cells. Herein we report that an **antisense** oligonucleotide targeted to a sequence unique to the alternatively spliced membrane-bound form of the HuIL-5Ralpha chain has been developed that selectively inhibits membrane, but not soluble, mRNA isoform expression. Both this membrane-specific oligonucleotide and an **antisense** oligonucleotide targeted to sequence common to both membrane and soluble isoforms were found to potently suppress cell surface IL-5Ralpha levels and **IL-5**-mediated cell survival by inducing apoptosis similar to **IL-5** withdrawal. Thus, these oligonucleotides represent unique genetic agents with therapeutic potential for diseases with an eosinophilic component.

L7 ANSWER 10 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 15
ACCESSION NUMBER: 1999:417007 BIOSIS
DOCUMENT NUMBER: PREV199900417007
TITLE: Adoptively transferred late allergic response is inhibited by IL-4, but not **IL-5**, **antisense** oligonucleotide.
AUTHOR(S): Molet, Sophie; Ramos-Barbon, David; Martin, James G.; Hamid, Qutayba (1)
CORPORATE SOURCE: (1) Meakins-Christie Laboratories, McGill University, 3626 St Urbain, Montreal, PQ, H2X 2P2 Canada
SOURCE: Journal of Allergy and Clinical Immunology, (July, 1999) Vol. 104, No. 1, pp. 205-214.
ISSN: 0091-6749.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: We have shown previously that the late airways response (LAR) can be transferred by ovalbumin-primed CD4+ T lymphocytes in Brown Norway rats. This response is associated with an increase of eosinophils and high expression of TH2 cytokines (IL-4 and **IL-5**) in bronchoalveolar lavage (BAL) fluid. Objective: In this study we hypothesized that the inhibition of IL-4 or **IL-5** production in the CD4+ cells transferred to a naive animal could decrease the LAR and prevent airway eosinophilia in response to antigen challenge. Methods: CD4+ cells, purified from the cervical lymph nodes of ovalbumin-sensitized rats, were maintained in culture for 6 hours with medium alone or with 10 mug/mL IL-4 **antisense** (AS), **IL-5** AS, or control AS oligodeoxynucleotide. Then the cells were administrated intraperitoneally to naive rats, which were challenged 2 days later by a 5 % ovalbumin aerosol. The lung resistance was measured for 8 hours, and then BAL was performed. Cytospin preparations from BAL cells were assessed for the presence of eosinophils by immunocytochemistry for major basic protein and for IL-4, **IL-5**, and IFN-gamma expression. Results: In rats injected with IL-4 AS-treated T cells, LAR, eosinophils, and IL-4 and **IL-5** expression were significantly decreased compared with the other groups. Only

IL-5 expression in BAL fluid was slightly decreased consequent to the transfer of **IL-5** AS-treated T cells. Conclusion: This study demonstrates that, in the CD4+ T cell-driven LAR, the early production of IL-4, but not **IL-5**, by the transferred CD4+ cells is essential for the development of the LAR.

L7 ANSWER 11 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 17

ACCESSION NUMBER: 1998:387225 BIOSIS
DOCUMENT NUMBER: PREV199800387225
TITLE: Role for Bcl-XL in delayed eosinophil apoptosis mediated by granulocyte-macrophage colony-stimulating factor and **interleukin-5**.
AUTHOR(S): Dibbert, Birgit; Daigle, Isabelle; Braun, Doris; Schranz, Corinna; Weber, Martina; Blaser, Kurt; Zangemeister-Wittke, Uwe; Akbar, Arne N.; Simon, Hans-Uwe (1)
CORPORATE SOURCE: (1) Swiss Inst. Allergy Asthma Res., Univ. Zurich, Obere Strasse 22, CH-7270 Davos Switzerland
SOURCE: Blood, (Aug. 1, 1998) Vol. 92, No. 3, pp. 778-783. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Eosinophils are potent inflammatory cells involved in allergic reactions. Inhibition of apoptosis of purified eosinophils by certain cytokines has been previously shown to be an important mechanism causing tissue eosinophilia. To elucidate the role of Bcl-2 family members in the inhibition of eosinophil apoptosis, we examined the expression of the known anti-apoptotic genes Bcl-2, Bcl-xL, and A1, as well as Bax and Bcl-xs, which promote apoptosis in other systems. We show herein that freshly isolated human eosinophils express significant amounts of Bcl-xL and Bax, but only little or no Bcl-2, Bcl-xs, or A1. As assessed by reverse transcription-polymerase chain reaction, immunoblotting, flow cytometry, and immunocytochemistry, we show that spontaneous eosinophil apoptosis is associated with a decrease in Bcl-xL mRNA and protein levels. In contrast, stimulation of the cells with granulocyte-macrophage colony-stimulating factor (GM-CSF) or **interleukin-5** (**IL-5**) results in maintenance or upregulation of Bcl-xL mRNA and protein levels. Moreover, Bcl-2 protein is not induced by GM-CSF or **IL-5** in purified eosinophils. Bcl-2 protein is also not expressed in tissue eosinophils as assessed by immunohistochemistry using two different eosinophilic tissue models. Furthermore, Bcl-xL **antisense** but not scrambled phosphorothioate oligodeoxynucleotides can partially block the cytokine-mediated rescue of apoptotic death in these cells. These data suggest that Bcl-xL acts as an anti-apoptotic molecule in eosinophils.

L7 ANSWER 12 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 18

ACCESSION NUMBER: 1998:434057 BIOSIS
DOCUMENT NUMBER: PREV199800434057
TITLE: Lyn, Jak2, and Raf-1 kinases are critical for the antiapoptotic effect of **interleukin 5**, whereas only Raf-1 kinase is essential for eosinophil activation and degranulation.
AUTHOR(S): Pazdrak, Konrad; Olszewska-Pazdrak, Barbara; Stafford, Susan; Garofalo, Roberto P.; Alam, Rafeul (1)
CORPORATE SOURCE: (1) Dep. Internal Med., Univ. Texas Med. Branch, Rt-0762, Galveston, TX 77555-0762 USA
SOURCE: Journal of Experimental Medicine, (Aug. 3, 1998) Vol. 188, No. 3, pp. 421-429. ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Interleukin (IL)-5** has been shown to

activate many signaling molecules in eosinophils, but their functional relevance remains unknown. We have examined the functional relevance of Lyn, Jak2, and Raf-1 kinases in eosinophil survival, upregulation of adhesion molecules and degranulation. To this goal we used Lyn and Raf-1 **antisense** (AS) oligodeoxynucleotides (ODN) to inhibit the expression of these proteins and tyrphostin AG490 to specifically block the activation of Jak2. We have demonstrated that all three kinases are important for **IL-5**-induced suppression of eosinophil apoptosis. However, Lyn and Jak2 tyrosine kinases are not important for the upregulation of CD11b and the secretion of eosinophil cationic protein. In contrast, Raf-1 kinase is critical for both these functions. This is the first identification of specific signaling molecules responsible for three important functions of eosinophils. We have established a central role for Raf-1 kinase in regulating eosinophil survival, expression of beta2 integrins and degranulation. Further, there appears to be a dissociation between two receptor-associated tyrosine kinases, i.e., Lyn and Jak2, and the activation of Raf-1 kinase. The delineation of the functional relevance of signaling molecules will help design therapeutic approaches targeting specific eosinophil function.

L7 ANSWER 13 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 20

ACCESSION NUMBER: 1998:434430 BIOSIS
DOCUMENT NUMBER: PREV199800434430
TITLE: In vivo expression of cytokine receptor mRNA in atopic dermatitis.
AUTHOR(S): Taha, Rame A.; Leung, Donald Y. M.; Ghaffar, Omar; Boguniewicz, Mark; Hamid, Qutayba (1)
CORPORATE SOURCE: (1) Meakins-Christie Lab., McGill Univ., 3626 St. Urbain St., Montreal, PQ H2X 2P2 Canada
SOURCE: Journal of Allergy and Clinical Immunology, (Aug., 1998) Vol. 102, No. 2, pp. 245-250. ISSN: 0091-6749.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease with immunopathologic features that vary depending on the duration of the lesion. Acute lesions are associated with a T-cell infiltrate and a high expression of IL-4 mRNA compared with chronic lesions, uninvolved AD skin, or skin from normal control subjects. Chronic lesions are rich in eosinophils and monocyte/macrophages and contain a greater number of **IL-5**, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-12 (p40) mRNA-positive cells. Objectives: In this study, we investigated the mRNA expression of the IL-4 receptor (IL-4Ralpha), IL-5Ralpha, GM-CSFRalpha, and IL12Rbeta2 in biopsy specimens from acute and chronic AD lesions, uninvolved AD skin, normal skin, and psoriatic skin lesions. Methods: Cytokine receptor mRNA was examined in paraformaldehyde-fixed biopsy specimens with in situ hybridization with specific **antisense** riboprobes. Results: Acute and chronic skin lesions exhibited a significant increase in numbers of IL-5Ralpha and GM-CSFRalpha mRNA-positive cells compared with uninvolved AD skin and normal skin ($P < .001$). Chronic skin lesions had a significantly greater number of IL-5Ralpha and GM-CSFRalpha mRNA-positive cells when compared with acute AD skin ($P < .001$). In contrast, IL-4Ralpha mRNA expression was increased in acute but not chronic AD lesions compared with uninvolved and normal skin ($P < .001$). No significant differences were observed in numbers of IL12Rbeta2 mRNA-positive cells when comparing acute AD, chronic AD, uninvolved AD, and normal skin. In psoriatic skin, the numbers of GM-CSFRalpha and IL-12Rbeta2 mRNA-positive cells were significantly increased compared with acute AD lesions, uninvolved skin, and normal control skin ($P < .01$). Conclusions: These results demonstrate that acute AD is associated with a high expression of IL-4Ralpha, whereas IL-5Ralpha and GM-CSFRalpha mRNA are predominantly increased in chronic AD and to lesser extent in acute lesions. These findings support the biphasic role

of IL-4, **IL-5**, and GM-CSF in the pathophysiology of AD.

L7 ANSWER 14 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 21

ACCESSION NUMBER: 1997:439617 BIOSIS
DOCUMENT NUMBER: PREV199799738820
TITLE: Src homology 2 protein tyrosine phosphatase (SHPTP2)/Src homology 2 phosphatase 2 (SHP2) tyrosine phosphatase is a positive regulator of the **interleukin 5** receptor signal transduction pathways leading to the prolongation of eosinophil survival.
AUTHOR(S): Pazdrak, Konrad; Adachi, Tetsuya; Alam, Rafeul (1)
CORPORATE SOURCE: (1) Univ. Texas Med. Branch, Dep. Internal Med., Rt-0672, Galveston, TX 77555-0762 USA
SOURCE: Journal of Experimental Medicine, (1997) Vol. 186, No. 4, pp. 561-568.
ISSN: 0022-1007.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Interleukin-5** (**IL-5**) regulates the growth and function of eosinophils. It induces rapid tyrosine phosphorylation of Lyn and jak2 tyrosine kinases. The role of tyrosine phosphatases in **IL-5** signal transduction has not been investigated. In this study, we provide first evidence that SH2 protein tyrosine phosphatase 2 (SHPTP2) phosphotyrosine phosphatase plays a key role in prevention of eosinophil death by **IL-5**. We found that **IL-5** produced a rapid activation and tyrosine phosphorylation of SHPTP2 within 1 min. The tyrosine phosphorylated SHPTP2 was complexed with the adapter protein Grb2 in **IL-5**-stimulated eosinophils. Furthermore, SHPTP2 appeared to physically associate with beta common (beta-c) chain of the **IL-5** receptor (IL5-beta-cR). The association of SHPTP2 with **IL-5**-beta-cR was reconstituted using a synthetic phosphotyrosine-containing peptide, beta-c 605-624, encompassing tyrosine (Y)-612. The binding to the phosphotyrosine-containing peptide increased the phosphatase activity of SHPTP2, whereas the same peptide with the phosphorylated Y-162 fwdarw F mutation did not activate SHPTP2. Only SHPTP2 **antisense** oligonucleotides, but not sense SHPTP2, could inhibit tyrosine phosphorylation of microtubule-associated protein kinase, and reverse the eosinophil survival advantage provided by **IL-5**. Therefore, we conclude that the physical association of SHPTP2 with the phosphorylated beta-c receptor and Grb2 and its early activation are required for the coupling of the receptor to the Ras signaling pathway and for prevention of eosinophil death by **IL-5**.

L7 ANSWER 15 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 22

ACCESSION NUMBER: 1997:250386 BIOSIS
DOCUMENT NUMBER: PREV199799549589
TITLE: IFN-gamma production from human Th1 cells is controlled by Raf kinase.
AUTHOR(S): Webber, Stephen (1); Zheng, Richard; Kamal, Ahmed; Withnall, Mike; Karlsson, Jan-Anders
CORPORATE SOURCE: (1) Rhone-Poulenc Rorer Ltd., Dagenham Res. Centre, Rainham Road South, Dagenham RM10 7XS UK
SOURCE: International Archives of Allergy and Immunology, (1997) Vol. 113, No. 1-3, pp. 275-278.
ISSN: 1018-2438.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Raf kinase is an important intracellular mediator in T cell signalling and may be crucial for the proliferation of this inflammatory cell. In order to elucidate its effect on cytokine production by human T cells in

response to T cell receptor activation, experiments were carried out on human T cell clones using **antisense** (AS) oligodeoxynucleotides (ODN) to inhibit the expression of Raf kinase. AS ODN to Raf were shown to have a significant effect on a human Th1-like T cell clone, inhibiting anti-CD3-induced IFN-gamma secretion by 76%, whereas no inhibitory effect was observed on **IL-5** or IL-4 production by a Th2-like clone. IL-2 secretion from both clones was also not affected by the Raf AS ODN. In all cases, a reduction in Raf kinase within the cell was demonstrated by Western blot. Our results clearly demonstrate the importance of Raf kinase in the production of IFN-gamma from Th1 cells, but also show the lack of effect of this intracellular mediator on cytokine (**IL-5**, IL-4) release from Th2 cells.

L7 ANSWER 16 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 23
ACCESSION NUMBER: 1997:88295 BIOSIS
DOCUMENT NUMBER: PREV199799380008
TITLE: **IL-5** but not interferon-gamma (IFN-gamma) inhibits eosinophil apoptosis by up-regulation of bcl-2 expression.
AUTHOR(S): Ochiai, K. (1); Kagami, M.; Matsumura, R.; Tomioka, H.
CORPORATE SOURCE: (1) Dep. Intern. Med., Toho Univ. Sch. Med., Sakura Hosp., 564-1 Shimoshizu, Sakura City, Chiba 285 Japan
SOURCE: Clinical and Experimental Immunology, (1997) Vol. 107, No. 1, pp. 198-204.
ISSN: 0009-9104.
DOCUMENT TYPE: Article
LANGUAGE: English
AB In order to determine regulatory mechanisms of eosinophil apoptosis, we examined the effect of recombinant **IL-5** and interferon-gamma (IFN-gamma) on eosinophil apoptosis and bcl-2 expression. rhIL-5 (2.5 ng/ml) significantly inhibited eosinophil apoptosis in 96h in vitro culture compared with medium only-cultured eosinophils (89.4 +- 3.6% versus 31.3 +- 12.2% (mean +- s.d.); n = 7, P lt 0.05). Further, rhIL-5 significantly increased bcl-2 protein and mRNA expression on cultured eosinophils. A phosphorothioate **antisense** oligonucleotide targeted at the ATG translation initiation codon of bcl-2 (10-5 M) could significantly block the supportive effect of rhIL-5 (0.25 ng/ml) for eosinophil survival compared with sense cDNA of bcl-2 on 96 h culture (inhibition rate 28.01 +- 4.56% versus 0.07 +- 1.73%; n = 4, P lt 0.05). In contrast, rhIFN-gamma (100 U/ml) significantly inhibited eosinophil apoptosis on 96 h in vitro culture (72.7 +- 10.5%; n = 7, P lt 0.05), but did not significantly up-regulate bcl-2 protein and mRNA. These results indicate that **IL-5** has inhibitory effects on eosinophil apoptosis by regulation of bcl-2 expression.

L7 ANSWER 17 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 24
ACCESSION NUMBER: 1998:121914 BIOSIS
DOCUMENT NUMBER: PREV199800121914
TITLE: **IL-5** and **IL-5** receptor in asthma.
AUTHOR(S): Kotsimbos, A. T. C.; Hamid, Q. (1)
CORPORATE SOURCE: (1) Dep. Med., Meakins-Christie Lab., McGill Univ., 3626 rue St. Urbain, Montreal, PQ H2X 2P2 Canada
SOURCE: Memorias do Instituto Oswaldo Cruz, (Dec. 30, 1997 (1998)) Vol. 92, No. SUPPL. 2, pp. 75-91.
ISSN: 0074-0276.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Eosinophils, along with mast cells are key cells involved in the innate immune response against parasitic infection whereas the adaptive immune response is largely dependent on lymphocytes. in chronic parasitic disease and in chronic allergic disease, **IL-5** is predominantly

a T cell derived cytokine which is particularly important for the terminal differentiation, activation and survival of committed eosinophil precursors. The human **IL-5** gene is located on chromosome 5 in a gene cluster that contains the evolutionary related IL-4 family of cytokine genes. The human **IL-5** receptor complex is a heterodimer consisting of a unique a subunit (predominantly expressed on eosinophils) and a beta subunit which is shared between the receptors for IL-3 & GM-CSF (more widely expressed). The alpha subunit is required for ligand-specific binding whereas association with the beta subunit results in increased binding affinity. The alternative splicing of the alphaIL-5R gene which contains 14 exons can yield several alphaIL-5R isoforms including a membrane-anchored isoform (alphaIL-5Rm) and a soluble isoform (alphaIL-5Rs). Cytokines such as **IL-5** produce specific and non-specific cellular responses through specific cell membrane receptor mediated activation of intracellular signal transduction pathways which, to a large part, regulate gene expression. The major intracellular signal transduction mechanism is activation of non-receptor associated tyrosine kinases including JAK and MAP kinases which can then transduce signals via a novel family of transcriptional factors named signal transducers and activators of transcription (STATS). JAK2, STAT1 and STAT5 appear to be particularly important in **IL-5** mediated eosinophil responses. Asthma is characterized by episodic airways obstruction, increased bronchial responsiveness, and airway inflammation. Several studies have shown an association between the number of activated T cells and eosinophils in the airways and abnormalities in FEV1, airway reactivity and clinical severity in asthma. It has now been well documented that **IL-5** is highly expressed in the bronchial mucosa of atopic and intrinsic asthmatics and that the increased **IL-5** mPNA present in airway tissues is predominantly T cell derived. Immunocytochemical staining of bronchial biopsy sections has confirmed that IL5 mRNA transcripts are translated into protein in asthmatic subjects. Furthermore, the number of activated CD4+ T cells and **IL-5** mRNA positive cells are increased in asthmatic airways following antigen challenge and studies that have examined **IL-5** expression in asthmatic subjects before and after steroids have shown significantly decreased expression following oral corticosteroid treatment in steroid-sensitive asthma but not in steroid resistant and chronic severe steroid dependent asthma. The link between T cell derived **IL-5** and eosinophil activation in asthmatic airways is further strengthened by the demonstration that there is an increased number of alphaIL-5R mRNA positive cells in the bronchial biopsies of atopic and non-atopic asthmatic subjects and that the eosinophil is the predominant site of this increased alphaIL-5R mRNA expression. We have also shown that the subset of activated eosinophils that expressed mRNA for membrane bound alphaIL5r inversely correlated with FEV1, whereas the subset of activated eosinophils that expressed mRNA for soluble alphaIL5r directly correlated with FEV1. Hence, not only does this data suggest that the presence of eosinophils expressing alphaIL-5R mRNA contribute towards the pathogenesis of bronchial asthma, but also that the eosinophil phenotype with respect to alpha IL5R isoform expression is of central importance. Finally, there are several animal, and more recently in vitro lung explant, models of allergen induced eosinophilia, late airway responses (LARS), and bronchial hyperresponsiveness (BHR) - all of which support a link between **IL-5** and airway eosinophila and bronchial hyperresponsiveness. The most direct demonstration of T cell involvement in LARS is the finding that these physiological responses can be transferred by CD4+ but not CD8+ T cells in rats. The importance of **IL-5** in animal models of allergen induced bronchial hyperresponsiveness has been further demonstrated by a number of studies which have indicated that **IL-5** administration is able to induce late phase responses and BHR and that anti-**IL-5** antibody can block allergen induced late phase responses and BHR. In summary, activated T lymphocytes, IL5 production and eosinophil activation are particularly important in the

asthmatic response. Human studies in asthma and studies in allergic animal models have clearly emphasized the unique role of **IL-5** in linking T lymphocytes and adaptive immunity, the eosinophil effector cell, and the asthma phenotype. The central role of activated lymphocytes and eosinophils in asthma would argue for the likely therapeutic success of strategies to block T cell and eosinophil activation (e.g. steroids). Importantly, more targeted therapies may avoid the complications associated with steroids. Such therapies could target key T cell activation proteins and cytokines by various means including blocking antibodies (e.g. anti-CD4, anti-CD40, anti-**IL-5** etc), **antisense** oligonucleotides to their specific mRNAs, and/or selective inhibition of the promoter sites.for these genes. Another option would be to target key eosinophil activation mechanisms including the alphaIL5r. As always, the risk to benefit ratio of such strategies await the results of well conducted clinical trials.

L7 ANSWER 18 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 27
ACCESSION NUMBER: 1992:119325 BIOSIS
DOCUMENT NUMBER: BA93:65125
TITLE: **INTERLEUKIN 5** MESSENGER RNA EXPRESSION BY EOSINOPHILS IN THE INTESTINAL MUCOSA OF PATIENTS WITH COELIAC DISEASE.
AUTHOR(S): DESREUMAUX P; JANIN A; COLOMBEL J F; PRIN L; PLUMAS J; EMILIE D; TORPIER G; CAPRON A; CAPRON M
CORPORATE SOURCE: CIBP, INST. PASTEUR, 1, RUE DU PR. A CALMATTE, B.P. 245, 59019 LILLE CEDEX, FRANCE.
SOURCE: J EXP MED, (1992) 175 (1), 293-296.
CODEN: JEMEAV. ISSN: 0022-1007.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB **Interleukin 5** (**IL-5**), the major factor involved in eosinophil differentiation, is produced by T cells or mast cells. In the present study, we found that eosinophils infiltrating the mucosa of four patients with active coeliac disease also express the **IL-5** mRNA. No positive signal was obtained in normal duodenum tissues and in the cell infiltrate from patients submitted to gluten restriction. The identification of labeled mucosal cells as eosinophils relied on their typical morphology. Moreover, highly purified blood eosinophils from three out of four patients with eosinophilia were also strongly labeled with the **IL-5 antisense** but not with the corresponding sense probe. Together, these results suggest that eosinophils have the capacity to synthesize **IL-5**, which could contribute to paracrine interactions with T and B cells and, in autocrine fashion, locally participate, through binding to the **IL-5** receptor, to eosinophil differentiation and activation. These data might have implications not only in the pathology of coeliac disease but also in other diseases associated with eosinophil infiltration.

L7 ANSWER 19 OF 40 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:137353 BIOSIS
DOCUMENT NUMBER: PREV200000137353
TITLE: Inhibition of GM-CSF, IL-3, and **IL-5** signalling by **antisense** oligodesoxynucleotide targeting the common beta chain receptor.
AUTHOR(S): Allam, M. (1); Renzi, P. M. (1)
CORPORATE SOURCE: (1) CHUM Research Center, University of Montreal, Montreal, PQ Canada
SOURCE: Journal of Allergy and Clinical Immunology., (Jan., 2000) Vol. 105, No. 1 part 2, pp. S298.
Meeting Info.: 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. San Diego, California, USA March 03-08, 2000 American Academy of Allergy, Asthma

and Immunology
. ISSN: 0091-6749.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L7 ANSWER 20 OF 40 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002106918 MEDLINE
DOCUMENT NUMBER: 21681712 PubMed ID: 11823534
TITLE: Lyn tyrosine kinase is important for **IL-5** -stimulated eosinophil differentiation.
AUTHOR: Stafford Susan; Lowell Clifford; Sur Sanjiv; Alam Rafeul
CORPORATE SOURCE: Department of Internal Medicine, Division of Allergy and Immunology, University of Texas Medical Branch, Galveston, TX 77555. Department of Laboratory Medicine, University of California, San Francisco, CA 94143.
CONTRACT NUMBER: PO1 AI46004 (NIAID)
R01 AI50179 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (2002 Feb 15) 168 (4) 1978-83.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020213
Last Updated on STN: 20020305
Entered Medline: 20020304

AB **IL-5** plays a pivotal role in growth and differentiation of eosinophils. The signal transduction mechanism of IL-5Ralpha is largely unknown. We have demonstrated that **IL-5** induces tyrosine phosphorylation of IL-5Ralpha in eosinophils. To identify IL-5Ralpha-associated tyrosine kinases, we have examined the expression of Src family tyrosine kinases in eosinophils. Among the Src family members, Lyn, Hck, Fgr, and Lck are present in eosinophils, and, among these four kinases, only Lyn is associated with the IL-5Ralpha under basal conditions. We also confirm the association of Janus kinase (Jak)2 with IL-5Ralpha. Lyn kinase phosphorylates both IL-5Ralpha and betacR in vitro. The importance of Lyn kinase for eosinophil differentiation was studied using **antisense** oligodeoxynucleotides. Lyn **antisense** oligodeoxynucleotide blocks eosinophil differentiation from stem cells in a dose-dependent manner. The Jak2 inhibitor tyrphostin AG490 also inhibits eosinophil differentiation. The importance of Lyn for eosinophil differentiation was further studied using Lyn knockout mice. The **IL-5**-stimulated eosinophil differentiation from bone marrow cells is significantly inhibited in Lyn(-/-) mice as compared with that in control mice. We conclude that both Lyn and Jak2 play an essential role in IL-5Ralpha signaling, leading to eosinophil differentiation. The effect of Lyn appears to be relatively specific for the eosinophilic lineage.

L7 ANSWER 21 OF 40 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002001343 MEDLINE
DOCUMENT NUMBER: 21621115 PubMed ID: 11751191
TITLE: **Interleukin**-4 and **interleukin-5** gene expression and inflammation in the mucus-secreting glands and subepithelial tissue of smokers with chronic bronchitis. Lack of relationship with CD8(+) cells.
AUTHOR: Zhu J; Majumdar S; Qiu Y; Ansari T; Oliva A; Kips J C; Pauwels R A; De Rose V; Jeffery P K
CORPORATE SOURCE: Department of Gene Therapy, Imperial College School of Medicine, London, United Kingdom.
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2001 Dec 15) 164 (12) 2220-8.

Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020128
Entered Medline: 20020125

AB We wished to determine if the inflammatory cells surrounding the airway mucus-secreting glands in chronic bronchitis (CB) were associated with **interleukin** (IL)-4 and **IL-5** mRNA expression and whether the CD8 T cell population expressed these cytokines. Digoxigenin-labeled IL-4 and **IL-5 antisense** RNA probes were used to detect gene expression in 11 asymptomic smokers (AS), 11 smokers with CB alone with normal lung function, and 10 smokers with chronic bronchitis and coexisting chronic obstructive pulmonary disease (CB+COPD; FEV(1)% of predicted of 43-77% and FEV(1)/ FVC of 51-68%). There were approximately three times as many IL-4 than **IL -5** mRNA(+) cells. The highest number of IL-4 mRNA(+) cells were in the submucosal glands of the CB group with normal lung function (216/mm(2)), significantly higher than the values in either the AS (63/mm(2)) or the CB+COPD (87/mm(2)) groups, respectively ($p < 0.01$). There were similar group differences when the total numbers of inflammatory cells were compared. Accordingly, there was a positive correlation between the number of IL-4 mRNA(+) cells and the total number of inflammatory cells in both the subepithelium and glandular compartments ($r = 0.60$; $p = 0.01$ and $r = 0.70$; $p = 0.02$, respectively). There were no significant associations between the numbers of CD8(+) and IL-4 or **IL-5** mRNA(+) cells. Of 1328 IL-4(+) and 1404 CD8(+) cells counted none was double labeled. Of 727 **IL-5**(+) and 1569 CD8(+) cells, none was double labeled. In contrast, as a positive control, 34% of tumor necrosis factor (TNF)-alpha(+) cells were also CD8(+) and 15% of CD8(+) cells were TNF-alpha positive. Thus, cells other than the CD8(+) phenotype produce IL-4 and **IL-5** in CB. We conclude that there is increased inflammation and IL-4 gene expression in the mucus-secreting glands and the airway mucosa of smokers with bronchitis: both are lower in those with CB and coexisting COPD suggesting that airway inflammation in CB is reduced when airway obstruction develops.

L7 ANSWER 22 OF 40 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001681753 MEDLINE
DOCUMENT NUMBER: 21584882 PubMed ID: 11727517
TITLE: **Interleukin-5**: a novel target for asthma therapy.
AUTHOR: Blumchen K; Kallinich T; Hamelmann E
CORPORATE SOURCE: Department of Paediatrics, Pulmonology and Immunology, Charite'-Campus-Virchow-Klinikum, Berlin, Germany.
SOURCE: Expert Opin Biol Ther, (2001 May) 1 (3) 433-53. Ref: 171
Journal code: 101125414. ISSN: 1471-2598.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020123
Entered Medline: 20011220

AB Eosinophilic airway inflammation is the main histologic correlate of airway hyper-responsiveness (AHR) and tissue injury in the pathogenesis of bronchial asthma. There is strong evidence for a central role of CD4+

T-cells secreting pro-allergic Th2-cytokines, such as IL-4 and **IL-5**, in the induction of airway eosinophilia and AHR. **IL-5** appears to be one of the main pro-inflammatory mediators among a growing number of cytokines and chemokines that induce, regulate and sustain eosinophilic airway inflammation. Animal studies provide confirmatory evidence for the important role of **IL-5** in the induction and maintenance of eosinophilic airway infiltration leading to altered airway function. Interfering with the action of **IL-5** represents one of the new immunomodulatory therapeutic strategies in the treatment of bronchial asthma. Compared to established immunosuppressive agents like steroids, a major advantage of this strategy is the specificity of reducing eosinophilic inflammation, thus possibly acting nearly without side effects. There are several possible ways to inhibit the effects of **IL-5** including alteration of the signalling pathway in the **IL-5** producing cell by inhibition or modification of transcription factors or the use of **antisense** oligonucleotides and blocking of the **IL-5** protein itself by monoclonal antibodies, soluble **IL-5** receptor or antagonists of the **IL-5** receptor expressed on the surface of eosinophils. Although preliminary data from the first clinical trials gave rise to skepticism about the efficacy of anti-**IL-5** treatment regarding the improvement of lung function of asthmatic patients, further studies with a better defined profile of the target population may provide encouraging results, allowing the introduction of this truly new therapeutic concept.

L7 ANSWER 23 OF 40 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2000261683 MEDLINE
DOCUMENT NUMBER: 20261683 PubMed ID: 10799906
TITLE: Inhibition of antigen-induced eosinophilia and late phase airway hyperresponsiveness by an **IL-5** **antisense** oligonucleotide in mouse models of asthma.
AUTHOR: Karras J G; McGraw K; McKay R A; Cooper S R; Lerner D; Lu T; Walker C; Dean N M; Monia B P
CORPORATE SOURCE: Departments of Molecular and Cellular Pharmacology and Pharmacology, Isis Pharmaceuticals, Carlsbad, CA 92008, USA.. jkarras@isisph.com
SOURCE: JOURNAL OF IMMUNOLOGY, (2000 May 15) 164 (10) 5409-15. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000607

AB Chronic airway eosinophilia is associated with allergic asthma and is mediated in part by secretion of **IL-5** from allergen-specific Th2 lymphocytes. **IL-5** is a known maturation and antiapoptotic factor for eosinophils and stimulates release of nascent eosinophils from bone marrow into the peripheral circulation. An **antisense** oligonucleotide found to specifically inhibit **IL-5** expression in vitro was observed to significantly reduce experimentally induced eosinophilia in vivo, in both the murine OVA lung challenge and allergic peritonitis models. Intravenous administration resulted in sequence-dependent inhibition of eosinophilia coincident with reduction of **IL-5** protein levels, supporting an **antisense** mechanism of action. Potent suppression of lung eosinophilia was observed up to 17 days after cessation of oligonucleotide dosing, indicating achievement of prolonged protection with this strategy. Furthermore, sequence-specific, **antisense** oligonucleotide-

mediated inhibition of Ag-mediated late phase airway hyperresponsiveness was also observed. These data underscore the potential utility of an **antisense** approach targeting **IL-5** for the treatment of asthma and eosinophilic diseases.

L7 ANSWER 24 OF 40 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2001045638 MEDLINE
DOCUMENT NUMBER: 20516018 PubMed ID: 11060690
TITLE: **IL-5**: biology and potential therapeutic applications.
AUTHOR: Weltman J K; Karim A S
CORPORATE SOURCE: Department of Medicine, Brown University School of Medicine, Providence, RI 02912, USA..
joel.weltman@brown.edu
SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2000 Mar) 9 (3) 491-6. Ref: 54
Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001204

AB **IL-5** is the predominant cytokine associated with antigen-induced eosinophilic inflammation in the lung. The activation of Th-2 cells leads to the production of **IL-5**. The pro-eosinophilic effects of **IL-5** include: (1) enhanced replication and differentiation of eosinophilic myelocytes; (2) enhanced degranulation of eosinophils; (3) prolonged survival time of eosinophils: and (4) enhanced adhesion of eosinophils. The effects of **IL-5** are mediated via the interaction of **IL-5** with receptors (IL-5R) that are expressed on the eosinophil cell membrane. Intracellular signalling produced by occupation of the IL-5R by **IL-5** occurs via the JAK-STAT system. **IL-5** is a 45 kDa glycoprotein consisting of two identical polypeptide chains. The 5'-promoter region of the **IL-5** gene contains elements that are down-regulated by glucocorticoids. Anti-**IL-5** reagents have the potential to suppress **IL-5** activity without the side effects of glucocorticoids. Studies using monoclonal antibodies (mAbs) against **IL-5** have established the feasibility of suppressing eosinophilic inflammation by specifically blocking **IL-5** activity. Studies with **antisense** **IL-5** are beginning to provide the basis for non-glucocorticoid, sequence-specific oligonucleotide inhibitors of **IL-5**. Research has begun on the development of mAbs and **antisense** oligonucleotide inhibitors of **IL-5** that can be inhaled and applied topically.

L7 ANSWER 25 OF 40 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 1998451425 MEDLINE
DOCUMENT NUMBER: 98451425 PubMed ID: 9780145
TITLE: Differential responsiveness of the **IL-5** and IL-4 genes to transcription factor GATA-3.
AUTHOR: Zhang D H; Yang L; Ray A
CORPORATE SOURCE: Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520, USA.
CONTRACT NUMBER: P50 HL56389 (NHLBI)
RO1 AI31137 (NIAID)
RO1 HL 56843 (NHLBI)
SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Oct 15) 161 (8) 3817-21.

Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981104

AB The cytokines IL-4 and **IL-5** are often coordinately produced by Th2 cells as in asthma. However, it is unclear whether similar molecular mechanisms underlie transcription of the two genes. We have previously shown that the transcription factor GATA-3 is expressed in Th2 but not Th1 cells and is crucial for activation of the **IL-5** promoter by different stimuli. In a different study, GATA-3 was shown to be sufficient for the expression of IL-4 and other Th2 cytokine genes. Here, we show that ectopic expression of GATA-3 is sufficient to drive **IL-5** but not IL-4 gene expression. Also, in Th2 cells, **antisense** GATA-3 RNA inhibits **IL-5** but not IL-4 promoter activation. The induction of **IL-5** gene expression by GATA-3 involves high affinity binding of GATA-3 to an inverted GATA repeat in the **IL-5** promoter.

L7 ANSWER 26 OF 40 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 1999018546 MEDLINE
DOCUMENT NUMBER: 99018546 PubMed ID: 9801738
TITLE: **Interleukin-5**: a proeosinophil cytokine mediator of inflammation in asthma and a target for **antisense** therapy.
AUTHOR: Weltman J K; Karim A S
CORPORATE SOURCE: Department of Medicine, Brown University School of Medicine, Providence, Rhode Island, USA.
SOURCE: ALLERGY AND ASTHMA PROCEEDINGS, (1998 Sep-Oct) 19 (5) 257-61. Ref: 42
Journal code: 9603640. ISSN: 1088-5412.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990120

AB **Interleukin-5** (**IL-5**) is the predominant cytokine associated with antigen-induced eosinophilic inflammation in the lung. The activation of TH2 cells leads to the production of **IL-5**. The proeosinophilic effects of **IL-5** include 1) enhanced replication and differentiation of eosinophilic myelocytes; 2) enhanced degranulation of eosinophils; 3) prolonged survival time of eosinophils; and 4) enhanced adhesion of eosinophils. The effects of **IL-5** are mediated via the interaction of **IL-5** with receptors (Il-5R) expressed on the eosinophil cell membrane. Intracellular signaling produced by occupation of the IL-5R by **IL-5** occurs via the JAK-STAT system. **IL-5** is a 45kD glycoprotein that consists of two identical polypeptide chains. The 5'-promoter region of the **IL-5** gene contains elements that are down-regulated by glucocorticoids. A 16-mer deoxyoligonucleotide, **antisense** to **IL-5** mRNA and with two phosphorothioate modifications, produced, at 20 micromolar concentration, complete inhibition of **IL-5** secretion by human peripheral blood mononuclear cells. The targeted 16-mer sequence of the

IL-5 mRNA did not display complete homology with any other known human gene sequences. These results suggest that the 16-mer phosphorothioate **antisense IL-5** provides the basis for a non-glucocorticoid, sequence-specific inhibitor of **IL-5**.

L7 ANSWER 27 OF 40 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 97098699 MEDLINE
DOCUMENT NUMBER: 97098699 PubMed ID: 8943376
TITLE: Deficient expression of p56(lck) in Th2 cells leads to partial TCR signaling and a dysregulation in lymphokine mRNA levels.
AUTHOR: al-Ramadi B K; Nakamura T; Leitenberg D; Bothwell A L
CORPORATE SOURCE: Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA.
CONTRACT NUMBER: GM40924 (NIGMS)
GM46367 (NIGMS)
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Dec 1) 157 (11) 4751-61.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19961227

AB Activation of T lymphocytes through their TCR is regulated by a delicate balance of phosphorylation and dephosphorylation of protein substrates by protein tyrosine kinases (PTKs) and phosphotyrosyl phosphatases, respectively. One of the earliest steps in the activation pathway is thought to involve the Src family PTKs, p56(lck) (Lck) and p59(fyn) (Fyn); however, the precise contribution of each PTK in TCR-mediated signaling remains incompletely understood. To study the role of Lck in mature T cells, **antisense** RNA was used to inhibit its expression in a nontransformed Th2 clone. In this report, we demonstrate that specific inhibition of Lck expression in Th2 cells, in the presence of normal levels of functional Fyn PTK, has profound consequences on multiple events following TCR stimulation, including an altered pattern of tyrosine-phosphorylated substrates, defective phosphorylation of TCR-zeta and ZAP-70, defective Ca2+ mobilization, and a approximately 90% reduction in proliferative responses to antigenic and mitogenic stimuli. In contrast, Lck-deficient cells expressed constitutively elevated levels of lymphokine mRNA, including IL-4, **IL-5**, and IL-10, and were capable of secreting IL-4 upon activation through the TCR. These results demonstrate a dissociation in functional responses in Lck-deficient Th2 cells and suggest a role for Lck in the induction of a state of T cell unresponsiveness.

L7 ANSWER 28 OF 40 MEDLINE
ACCESSION NUMBER: 2001678769 MEDLINE
DOCUMENT NUMBER: 21581601 PubMed ID: 11724761
TITLE: **Interleukin-5** in growth and differentiation of blood eosinophil progenitors in asthma: effect of glucocorticoids.
AUTHOR: Kuo H P; Wang C H; Lin H C; Hwang K S; Liu S L; Chung K F
CORPORATE SOURCE: Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Dec) 134 (7) 1539-47.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011129
Last Updated on STN: 20020125
Entered Medline: 20020114

AB 1. There are increased numbers of circulating CD34(+) progenitor cells for eosinophils in patients with atopic asthma, with a further increase following allergen exposure or spontaneous worsening of asthma. We investigated the expression of **IL-5** and IL-5Ralpha receptor in circulating CD34(+) progenitor cells in allergic asthmatics and the effects of corticosteroids. 2. Using double-staining techniques, up to 50% of CD34(+) cells expressed intracellular **IL-5**, and by RT - PCR, there was significant expression of **IL-5** mRNA. When cultured in a semi-liquid methylcellulose medium, there were more eosinophil colony-forming units grown from asthmatic non-adherent mononuclear cell depleted of T cells in the presence of the growth factors GM-CSF, SCF and IL-3, but not of **IL-5**. 3. An anti-IL-5Ralpha receptor antibody and an anti-sense **IL-5** oligonucleotide reduced the number of eosinophil colony forming units. No **IL-5** mRNA or protein expression on T cells was observed in asthmatics or normal subjects. In the presence of growth factors including **IL-5**, there were significantly greater colony numbers with eosinophilic lineage grown from either asthmatics or normal subjects. 4. Dexamethasone (10(-6) M) suppressed **IL-5** mRNA and protein expression in CD34(+) cells, and reduced eosinophil colony-forming units in asthmatics, but not in normal subjects. Dexamethasone did not change the expression of IL-5Ralpha on CD34(+) cells. 5. We conclude that there is increased expression of **IL-5** on blood CD34(+) cells of patients with asthma and that this expression may auto-regulate eosinophilic colony formation from these progenitor cells. Corticosteroids inhibit the expression of **IL-5** in circulating CD34(+) progenitor cells.

L7 ANSWER 29 OF 40 MEDLINE
ACCESSION NUMBER: 1999323991 MEDLINE
DOCUMENT NUMBER: 99323991 PubMed ID: 10395690
TITLE: A novel Lyn-binding peptide inhibitor blocks eosinophil differentiation, survival, and airway eosinophilic inflammation.
AUTHOR: Adachi T; Stafford S; Sur S; Alam R
CORPORATE SOURCE: Department of Internal Medicine, Division of Allergy and Immunology, University of Texas Medical Branch, Galveston 77555, USA.
CONTRACT NUMBER: AI135713 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Jul 15) 163 (2) 939-46.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 20000303
Entered Medline: 19990729

AB Receptor antagonists block all receptor-coupled signaling pathways indiscriminately. We introduce a novel class of peptide inhibitors that is designed to block a specific signal from a receptor while keeping other signals intact. This concept was tested in the model of **IL-5** signaling via Lyn kinase. We have previously mapped the Lyn-binding site of the **IL-5**/GM-CSF receptor common beta (beta c) subunit. In the present study, we designed a peptide inhibitor using the Lyn-binding sequence. The peptide was N-stearated to enable cellular internalization. The stearated peptide blocked the binding of Lyn to the beta c receptor and the activation of Lyn. The lipopeptide

did not affect the activation of Janus kinase 2 or its association with beta c. The inhibitor blocked the Lyn-dependent functions of **IL-5** in vitro (e.g., eosinophil differentiation from stem cells and eosinophil survival). It did not affect eosinophil degranulation. When applied in vivo, the Lyn-binding peptide significantly inhibited airway eosinophil influx in a mouse model of asthma. The lipopeptide had no effect on basophil histamine release or on the proliferation of B cells and T cells. To our knowledge, this is the first report on an inhibitor of **IL-5** that blocks eosinophil differentiation, survival, and airway eosinophilic inflammation. This novel strategy to develop peptide inhibitors can be applied to other receptors.

L7 ANSWER 30 OF 40 MEDLINE
ACCESSION NUMBER: 1999244146 MEDLINE
DOCUMENT NUMBER: 99244146 PubMed ID: 10229140
TITLE: T(H)1 cytokines are produced in labial salivary glands in Sjogren's syndrome, but also in healthy individuals.
AUTHOR: Konttinen Y T; Kemppinen P; Koski H; Li T F; Jumppanen M; Hietanen J; Santavirta S; Salo T; Larsson A; Hakala M; Sorsa T
CORPORATE SOURCE: Department of Anatomy, Institute of Biomedicine, University of Helsinki, Finland.
SOURCE: SCANDINAVIAN JOURNAL OF RHEUMATOLOGY, (1999) 28 (2) 106-12. Journal code: 0321213. ISSN: 0300-9742.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990513

AB The aim of the present study was to assess the T cell cytokines IFN-gamma, IL-2, IL-4 and **IL-5** in labial salivary glands (LSG) in Sjogren's syndrome (SS) and healthy controls using RT-PCR and immunohistochemistry. IFN-gamma is always or almost always produced in SS and in healthy controls. IL-2 was also found in some samples, but IL-4 and **IL-5** were not. Less than 2% of all inflammatory mononuclear cells contained immuoreactive IFN-gamma or IL-2. Cytokine mRNA profile in LSGs in SS is skewed towards a T(H)1 pattern. The classical T(H)1 cytokines are also produced in normal glands, even in the absence of foci. T(H)1 type response may play an active role as part of the mucosal associated lymphoid tissue/responses, perhaps in prevention of reactivation of latent viruses. This may also make the exocrine glands a locus minoris resistentiae when the self tolerance is broken.

L7 ANSWER 31 OF 40 MEDLINE
ACCESSION NUMBER: 96261643 MEDLINE
DOCUMENT NUMBER: 96261643 PubMed ID: 8666899
TITLE: Requirement of Lyn and Syk tyrosine kinases for the prevention of apoptosis by cytokines in human eosinophils.
AUTHOR: Yousefi S; Hoessli D C; Blaser K; Mills G B; Simon H U
CORPORATE SOURCE: Swiss Institute of Allergy and Asthma Research, University of Zurich, Switzerland.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Apr 1) 183 (4) 1407-14. Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 20000303

Entered Medline: 19960805

AB In allergic diseases, the cytokines **interleukin** (**IL**) **5** and granulocyte/macrophage colony-stimulating factor (GM-CSF) are upregulated and have been proposed to cause blood and tissue eosinophilia by inhibition of eosinophil apoptosis. We demonstrate herein, in freshly isolated human eosinophils, that the IL-3/**IL-5**/GM-CSF receptor beta subunit interacts with cytoplasmic tyrosine kinases to induce phosphorylation of several cellular substrates, including the beta subunit itself. The Lyn and Syk intracellular tyrosine kinases constitutively associate at a low level with the IL-3/**IL-5**/GM-CSF receptor beta subunit in human eosinophils. Stimulation with GM-CSF or **IL-5** results in a rapid and transient increase in the amount of Lyn and Syk associated with the IL-3/**IL-5**/GM-CSF receptor beta subunit. Lyn is required for optimal tyrosine phosphorylation and activation of Syk. In contrast, Syk is not required for optimal tyrosine phosphorylation and activation of Lyn. These data suggest that Lyn is proximal to Syk in a tyrosine kinase cascade that transduces IL-3, **IL-5**, or GM-CSF signals. Compatible with this model, both Lyn and Syk are essential for the activation of the antiapoptotic pathway(s) induced through the IL-3/**IL-5**/GM-CSF receptor beta subunit in human eosinophils.

L7 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 26
ACCESSION NUMBER: 1995:616304 CAPLUS
DOCUMENT NUMBER: 123:80580
TITLE: The role of Bcl-2 protein and autocrine growth factors in a human follicular lymphoma-derived B cell line
AUTHOR(S): Blagosklonny, Mikhail V.; Neckers, Leonard M.
CORPORATE SOURCE: Clinical Pharmacology Branch, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Eur. Cytokine Network (1995), 6(1), 21-7
CODEN: ECYNEJ; ISSN: 1148-5493
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have shown that the ability of the human follicular lymphoma-derived cell line SU-DHL-6 to proliferate and survive in vitro depends on both Bcl-2 expression and multiple autocrine growth factors. Treatment with Bcl-2 **antisense** (AS Bcl-2) decreased Bcl-2 protein levels. However, a cytotoxic effect was seen only at very restricted cell densities. Below such densities cells underwent spontaneous death without any treatment, while above these cell densities no cytotoxic effect of AS Bcl-2 could be seen. The conditioned medium of SU-DHL cells supported the survival and growth of these cells cultivated at low cell densities and partially reversed the cytotoxicity assocd. with Bcl-2 depletion. RT/PCR anal. revealed autocrine expression of IL-1.beta., IL-2, **IL-5**, and TNF-.beta. in SU-DHL cells. Neutralizing antibodies against these cytokines inhibited SU-DHL proliferation. Thus, development of autocrine GF secretion may be the second step in the pathogenesis of follicular lymphomas.

L7 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:635924 CAPLUS
DOCUMENT NUMBER: 135:194487
TITLE: Methods of prevention and treatment of asthma and allergic conditions
INVENTOR(S): Sukurkovich, Boris; Skurkovich, Simon
PATENT ASSIGNEE(S): Advanced Biotherapy, Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062287	A1	20010830	WO 2001-US5660	20010223

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2000-511972 A 20000224

AB The present invention relates to allergy vaccines and methods of treating and/or preventing asthma, and allergic conditions. The invention is based on the discovery that inhibiting the ligand/receptor interactions involving, e.g., IgE, IL-3, IL-4, **IL-5**, IL-6, IL-10, IL-13, interferon-alpha, histamine, leukotriene, and their resp. receptors, inhibits prodn. of IgE thereby treating or preventing such diseases or conditions. Competitive inhibition of such receptor/ligand interactions is accomplished by immunizing a human or veterinary patient with the **interleukin**, interferon-alpha, histamine, leukotriene, their receptors, in any combination. Also, the invention relates to inhibiting receptor/ligand interactions involved in IgE prodn. by competitively inhibiting such interactions by administering antibodies to the ligands, receptors, or both, as well as by administering analogs of the receptors (e.g., sol. receptors not assocd. with a cell).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:115296 CAPLUS
DOCUMENT NUMBER: 134:177367
TITLE: Cloning of canine **interleukin 5** cDNA and its therapeutic use
INVENTOR(S): Guo, Hongliang; Lawton, Robert; Mermer, Brion; Aiyappa, Ashok P.
PATENT ASSIGNEE(S): Idexx Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001011049	A2	20010215	WO 2000-US21651	20000809
WO 2001011049	A3	20020307		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-371615 A 19990810

AB The present invention provides for the isolation and characterization of canine **interleukin-5** (**IL-5**) and nucleic acid and amino acid sequences of **IL-5**. More particularly, recombinant DNA mols. encoding for canine **interleukin-5** and conservative variants are provided. In other aspects, the invention provides cells comprising the recombinant vectors, and methods for producing canine **IL-5** comprising the steps of inserting a transcription regulatory sequence proximal to the **IL-5** gene in a cell comprising that gene, and stimulating prodn. of **IL-5** through the regulatory sequence. Methods of prepg. antibodies against canine

IL-5 mimetopes (using phage display technol.), using **antisense** mols. (blocking **IL-5** mRNA) or **IL-5** peptides (interfering **IL-5** receptor binding) to inactivate **IL-5** expression and function for dog allergy treatment are provided as well.

L7 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:240109 CAPLUS
DOCUMENT NUMBER: 134:275750
TITLE: Alteration of cellular proliferation or apoptosis by **antisense** modulation of mRNA splicing, polyadenylation, or degradation
INVENTOR(S): Bennett, C. Frank; Cooke, Stanley T.; Manoharan, Muthiah; Wyatt, Jacqueline R.; Baker, Brenda F.; Monia, Brett P.; Freier, Susan M.; McKay, Robert; Karras, James G.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 39 pp., Cont.-in-part of U.S. Ser. No. 167,921.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6210892	B1	20010403	US 1999-277020	19990326
US 6172216	B1	20010109	US 1998-167921	19981007
US 6214986	B1	20010410	US 1999-323743	19990602
WO 2000020432	A1	20000413	WO 1999-US22448	19990928
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9962710	A1	20000426	AU 1999-62710	19990928
EP 1119579	A1	20010801	EP 1999-949943	19990928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001007025	A1	20010705	US 2000-734846	20001212
US 2002049173	A1	20020425	US 2000-734847	20001212

PRIORITY APPLN. INFO.:
US 1998-167921 A2 19981007
US 1999-277020 A2 19990326
US 1999-323743 A 19990602
WO 1999-US22448 W 19990928

AB The present invention provides compns. and methods for controlling the behavior of a cell, tissue or organism through **antisense** modulation of mRNA processing, using **antisense** compds. which do not support cleavage of the mRNA target. **Antisense** oligonucleotides with 2'-methoxyethoxy (2'-MOE), 2'-dimethylaminooxyethoxy (2'-DMAOE), 2'-dimethylaminoethoxyethoxy, 2'-acetamide, morpholino or peptide nucleic acid modifications were synthesized with phosphodiester or phosphorothioate backbone linkages. The modifications of **antisense** oligonucleotides were either uniform or gapped. Effects of modified **antisense** oligonucleotides on mRNAs were detd. for **interleukin 5** (**IL-5**) receptor .alpha. and Bcl-x. Uniformly 2'-MOE oligonucleotides targeted to certain exons or intron/exon boundaries of the sol./membrane **IL-5** receptor .alpha. caused reduced expression of the membrane form and increased expression of the sol. form. Reduced cell surface

expression of **IL-5** receptor .alpha. protein, induction of apoptosis, and inhibition of cell proliferation in response to **IL-5** by the 2'-MOE **antisense** oligonucleotides were also measured. The Bcl-xl (long) isoform of Bcl-x inhibits apoptosis while the Bcl-xs (short) isoform antagonizes Bcl-xl. Uniformly 2'-MOE, phosphorothioate oligonucleotides (e.g. ISIS 22783) targeted to a region upstream of the 5' splice site of bcl-xl were found to increase the ratio of bcl-xs to bcl-xl. After **antisense** treatment with the highly active ISIS 22783, increased apoptosis of cells in response to UV stress, cisplatinum-induced cell death and taxol-induced cell death were quantitated. An ISIS 22783 analog with 2'-DMAOE had a similar effect on the bcl-xs/bcl-xl mRNA ratio.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:262806 CAPLUS
TITLE: **Interleukin-5**
AUTHOR(S): Henry, N. Lynn; Nutman, Thomas B.
CORPORATE SOURCE: Helminth Immunology Section and Clinical Parasitology Unit, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
SOURCE: Cytokine Therapeutics in Infectious Diseases (2001), 45-63. Editor(s): Holland, Steven M. Lippincott Williams & Wilkins: Philadelphia, Pa.
CODEN: 69CLJL; ISBN: 0-7817-1625-X
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review summarizes the current knowledge on the structure and function of **interleukin (IL)-5**, regulation of the gene encoding this cytokine, the interaction of the mol. with its receptor, and its biol. role in selected infectious disease states. The therapeutic strategies that could involve the use of **IL-5** or **IL-5** blockade either by specific anti-**IL-5** antibodies, sol. receptors, or **antisense** oligonucleotides are discussed.
REFERENCE COUNT: 195 THERE ARE 195 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:238402 CAPLUS
DOCUMENT NUMBER: 132:274328
TITLE: Inhibition of expression of **interleukin-5** with **antisense** oligonucleotide containing at least one non-natural internucleoside linkage
INVENTOR(S): Weltman, Joel K.; Karim, Aftab S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6048726	A	20000411	US 1998-79839	19980515

AB A method of inhibiting **interleukin-5** expression uses an **antisense** oligonucleotide which contains at least one non-natural internucleoside linkage. A 16-mer **antisense** oligonucleotide, 5'-ACT*CAAAT*GCAGAAGC-3' (* indicated PS linkage), at 20

.mu.M completely inhibited **IL-5** secretion by human primary peripheral blood mononuclear cells.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:149780 CAPLUS
DOCUMENT NUMBER: 116:149780
TITLE: Growth factor-dependent inhibition of normal hematopoiesis by N-ras **antisense** oligodeoxynucleotides
AUTHOR(S): Skorski, Tomasz; Szczylik, Cezary; Ratajczak, Mariusz Z.; Malaguarnera, Lucia; Gewirtz, Alan M.; Calabretta, Bruno
CORPORATE SOURCE: Jefferson Cancer Inst., Thomas Jefferson Univ., Philadelphia, PA, 19107, USA
SOURCE: J. Exp. Med. (1992), 175(3), 743-50
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To det. whether N-ras expression is required at specific stages of the process of in vitro normal human hematopoiesis, adherent- and T lymphocyte-depleted mononuclear marrow cells (A-T-MNC) or highly purified progenitors (CD34+ cells) were cultured in semisolid medium, under conditions that favor the growth of specific progenitor cell types, after exposure to N-ras sense and **antisense** oligodeoxynucleotides. N-ras **Antisense**, but not sense, oligodeoxynucleotide treatment of A-T-MNC and CD34+ cells resulted in a decreased no. of granulocyte/macrophage colony-forming units (CFU-GM) induced by **interleukin** 3 (IL-3) or granulocyte/macrophage colony-stimulating factor (GM-CSF) and of macrophage colonies (CFU-M) induced by M-CSF, but not of granulocytic colonies induced with G-CSF or **IL-5** . However, the same treatment inhibited colony formation induced by each of the above factors in combination with IL-3. Megakaryocytic colony (CFU-Meg) formation from A-T-MNC or CD34+ cells in the presence of IL-6 + IL-3 + erythropoietin (Epo) was also markedly decreased after **antisense** oligodeoxynucleotide treatment. Erythroid colonies derived from A-T-MNC in the presence of Epo (CFU-E) were not inhibited upon **antisense** treatment, whereas those arising from A-T-MNC or CD34+ cells in the presence of IL-3 + Epo (BFU-E) were markedly affected. Thus, distinct signal transduction pathways, involving N-ras or not, are activated by different growth factors in different hematopoietic progenitor cells.

L7 ANSWER 39 OF 40 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001009738 EMBASE
TITLE: **Interleukin-5**: A drug target for allergic diseases.
AUTHOR: Sanderson C.J.; Urwin D.
CORPORATE SOURCE: C.J. Sanderson, Dept. of Molecular Immunology, Western Australian Inst. Med. Res., Curtin University of Technology, Rear 50 Murray Street, Perth 6000, WA, Australia. colin@cyllene.uwa.edu.au
SOURCE: Current Opinion in Investigational Drugs, (2000) 1/4 (435-441).
Refs: 54
ISSN: 0967-8298 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
015 Chest Diseases, Thoracic Surgery and Tuberculosis
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
030 Pharmacology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB There is a large body of evidence that eosinophils are a key component of the allergic response in asthma. **Interleukin** (**IL**) **5** is uniquely involved in the production of eosinophils, and with a variety of other cytokines and factors controls their activation, localization and survival. Thus, **IL-5** is an important drug target for new anti-asthmatics. The routes to drug discovery are based on screens for inhibitors of **IL-5** production, ligand antagonists, control of receptor expression and receptor activation. In this review, we will discuss specific targets and screening assays with examples of some of the compounds in development.

L7 ANSWER 40 OF 40 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91232690 EMBASE
DOCUMENT NUMBER: 1991232690
TITLE: In vitro immunization of human B lymphocytes. MAPPing of lymphokine specific mRNA and the effect of recombinant factors.
AUTHOR: Simonsson A.C.; Larrick J.W.; Borrebaeck C.A.K.
CORPORATE SOURCE: Department of Immunotechnology, Lund University, P.O. Box 7031, S-220 07 Lund, Sweden
SOURCE: Human Antibodies and Hybridomas, (1991) 2/3 (148-154).
ISSN: 0956-960X CODEN: HANHEX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The kinetics of lymphokine-specific DNA transcription during in vitro immunization of human peripheral blood lymphocytes and splenocytes were studied using the polymerase chain reaction. The levels of specific mRNA were shown to be downregulated by cytolytic L-leucyl-leucine methyl ester-sensitive lymphocytes. In in vitro immunizations using L-leucyl-leucine methyl ester-treated human PBL or splenocytes, the lymphokine mRNA expression pattern indicated an active gene transcription during the entire stimulation period, especially for the IL-2 and **IL-5** genes. Transcription of IL-6 and TNF.beta. started on day 4, whereas IFN.gamma. mRNA reached its maximum level on day 4. In vitro immunizations of cells not treated with L-leucyl-leucine methyl ester revealed a transient transcription of lymphokine DNA that was declining already after day 2. Exogenously added recombinant IL-2, IL-4, and IL-6 all exhibited a positive immunoregulatory effect on Ig secretion, whereas **IL-5** was not found to have any effect on immunoglobulin secretion during the in vitro culture. These results present the first information useful for designing in vitro immunization systems based on recombinant lymphokines and **antisense** DNA for gene regulation.